

Rejection Under 35 U.S.C. § 103(a)

Claims 23-58 remain rejected as unpatentable under 35 U.S.C. § 103(a) over Sugiura, K. and H.M. Wuest “Effect of Thalidomide on Transplantable Mouse, Rat, and Hamster Tumors” *GANN*, 55, 57-60, February 1964 (“Sugiura”) or over United States Patent No. 5,399,363 to Liversidge et. al. (“Liversidge”). The Examiner maintains that the mere contention in Sugiura that repeated interperitoneal injections of thalidomate (1000 mg/kg/day) had a *moderately inhibitory* effect on only one tumor model — namely, lewis bladder carcinoma — is sufficient to render the claims obvious despite the fact that *twenty-four* other tumors were reported to be non-responsive to thalidomide. Applicant respectfully traverses the Examiner’s rejection below and provide additional evidence of non-obviousness.

Applicant claims a method of inhibiting tumor formation and a method of inhibiting tumor metastasis using an angiogenesis-inhibiting amount thalidomide. Contrary to the Examiner’s contention, Sugiura teaches away from the method of inhibiting tumor formation as claimed by the Applicant. On page 59, Sugiura states “Thalidomide had no inhibitory effect on the growth of 18 kinds of mouse, rat, and hamster tumor.” Sugiura further teaches that thalidomide only had *slight inhibiting effect* on six of the tumors treated and only had *moderate inhibition* of one tumor at 1000mg/kg/day. Given the overall teaching away of Sugiura, the Examiner’s rejection is legally improper and should be withdrawn. Indeed, given Sugiura’s teaching, it does not and cannot provide a reasonable expectation of success. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988).

Further, Applicant respectfully submits that the Applicant’s interpretation of Sugiura is consistent with those of skill in the art at the relevant time. To that end, Applicant respectfully requests the Examiner consider the disclosure of H. Mükter, “Thalidomide and Tumor” *Antimicrobial Agents and Chemotherapy* 1965, 531-538, (“Mükter”) enclosed herewith as Exhibit A. As the Examiner will see, Mükter describes Sugiura as showing *no effect* on twenty-four tumors of mouse, rat and hamster and as only having a *weak* effect for Lewis Bladder-carcinoma. Clearly, the are recognized that Sugiura demonstrated that thalidomide was *not active* against cancer. Thus, this reference cannot support the Examiner’s obviousness rejection.

Significantly, other arguably more relevant studies in humans also teach away from Applicant’s claimed invention in that they show little or no activity for thalidomide against tumors. Applicant directs the Examiner’s attention to Grabstald and Golbey “Clinical

experiences with thalidomide in patients with cancer”, *Clinical Pharmacology and Therapeutics*, 6, 298-302, 1965 (“Grabstald”) enclosed herewith as Exhibit B.¹ Grabstald observed the effects of thalidomide in 71 patients with a variety of cancers. Grabstald concludes, at page 301, “in the absence of more definite evidence of pharmacologic or anticancer effects in man, *we conclude that further random trials of this drug against cancer in man are not indicated.*” In sum, one of skill in the art, in light of the disclosures of Mükter and Grabstald, would not find the disclosure of Suguira to provide the requisite suggestion of, much less the expectation of success in the mere description of a weak effect on one cancer in Suguira.

Liversidge does not remedy the deficiencies of Suguira. The Examiner has relied on Column 3, lines 46-49 of the Liversidge patent in alleging that the claims are obvious. The Examiner contends that Liversidge’s contention that “the anticancer agent can be an immunosuppressive drug, such as, for example, cyclosporine, azathioprine, sulfasalazine, methoxsalen, and thalidomide” renders Applicant’s method of inhibiting tumor formation using an angiogenesis-inhibiting amount thalidomide obvious. Applicant maintains that this statement does not suggest all the claim limitations nor satisfy the legal requirement for obviousness.

At the time of Liversidge, thalidomide was not known to be an anticancer agent. Liversidge’s misleading statement does not change that fact. At the relevant time, each of the compounds referred to by Liversidge were merely immunosuppressive agents. According to The Merck Index, thalidomide was at the time and after Liversidge’s disclosure therapeutically classified only as an immunomodulatory compound and a sedative [*The Merck Index*, 12th ed., Whitehouse Station: Merck, 1996]. Neither of these therapeutic uses teach or would suggest that thalidomide would have anticancer activity. Significantly, nowhere in Liversidge are the immunosuppressive compounds specifically shown to be effective as anticancer agents. The mere statement that an “anticancer agent can be an immunosuppressive drug” does not provide an adequate suggestion of Applicant’s method of inhibiting tumor formation using an angiogenesis-inhibiting amount thalidomide, much less provide the requisite suggestion of the dosages or for the specific tumors claimed by the Applicant.

¹ Applicant respectfully requests the Examiner execute the enclosed PTO Form 1449 in order to demonstrate that these references were considered.

Further, Liversidge must be read in the context of Suguira, Mükter, Grabstald and other art at the time. *In re Ochiai*, 71 F.3d 1565, 1569, 37 USPQ2d 1127, 1131 (Fed.Cir.1995). As shown above, Suguira, Mükter and Grabstald teach away from Applicant's invention. Liversidge does not provide any evidence to the contrary. Thus, Liversidge alone, or in combination with Sugiura, does not render the invention obvious.

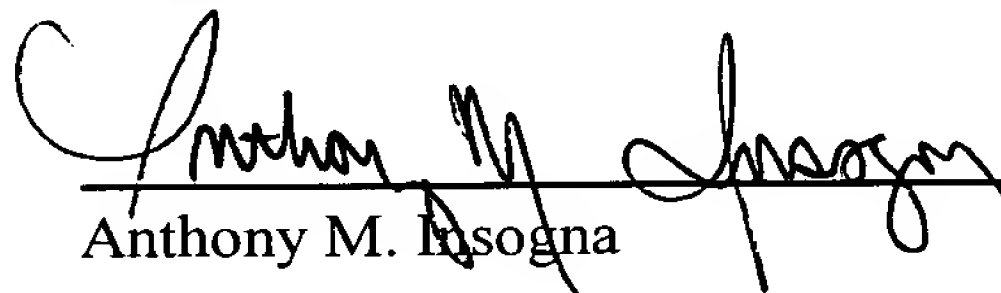
Finally, the mere allegation in Liversidge does not provide a reasonable expectation of success. *In re Fine*, 837 F.2d 1071, 1075, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Even if one were to choose an immunosuppressive drug from the list for incorporation into Liversidge's particles, there is no teaching to suggest that they will be effective to have angiogenesis inhibiting effects for inhibition of tumor growth. In sum, Liversidge, at best, suggests that immunosuppressive agents can be tried in Liversidge's delivery method -- not for cancer. Even assuming, *arguendo*, that Liversidge's statement was accurate it merely provides an invitation to experiment. As the Examiner knows, "obvious to try" is not the proper legal standard. *In re O'Farrel* 853 F.2d 894, 57 USLW 2147, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988). In sum, this unsupported allegation fails to provide the requisite legal suggestion plus reasonable expectation of success, but also is premised on unsound scientific basis. Immunosuppressive agents are not antitumor agents. Applicant therefore respectfully submits that claims 23-57 are not obvious over Liversidge. Accordingly, Applicant respectfully requests that the Examiner withdraw the rejection of claims 23-57 under 35 U.S.C. §103(a).

Conclusion

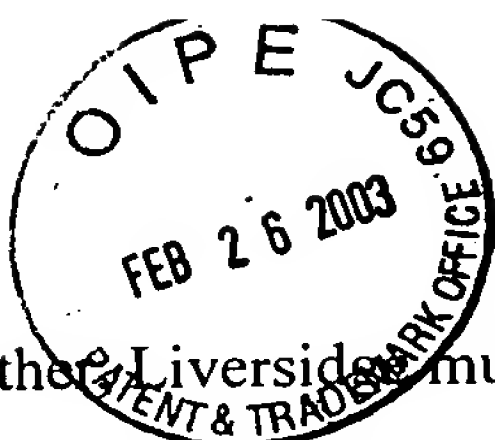
Applicant respectfully requests that the above remarks and accompanying documents be entered in the present application file. Applicant also respectfully requests withdrawal of the outstanding rejections. An early allowance of the present application is respectfully requested. No fee is believed due. However, if the Examiner determines that any fee is due, please charge the required fee to Pennie & Edmonds LLP Account No. 16-1150.

Respectfully submitted,

Date: February 26, 2003

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Enclosures



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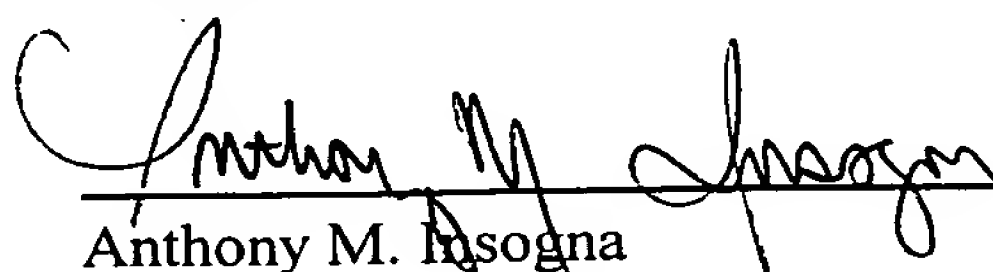
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